UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/749,962	12/31/2003	Chandrika Govardhan	ALTUS-4	2164

1473 7590 05/03/2007

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1211 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-8704

EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1656	

MAIL DATE	DELIVERY MODE
05/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/749,962	GOVARDHAN ET AL.	
	Examiner	Art Unit	
	Suzanne M. Noakes, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,7-10 and 17-65* is/are pending in the application.

4a) Of the above claim(s) *23-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,7-10,17-22 and 60-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The amendment to the claims and specification filed under 37 C.F.R. § 1.111 filed 05 February 2007 is acknowledged. Applicants have cancelled claims 1-3, 5-6 and 11-16 and added new claims 60-65. Thus, claims 4, 7-10 and 17-65 are pending and claims 23-59 are withdrawn at this time from further consideration as they are drawn to non-elected subject matter but *may* be subject to rejoinder at a later time (see MPEP § 821.04). Claims 4, 7-10, 17-22 and new claims 60-65 are subject to examination on the merits.

Withdrawal of Rejections/Objections

2. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

It is specially noted that the objection to the specification for improper numbering of the Tables is withdrawn as the Examiner inadvertently missed Table 15 on the bottom of page 67.

3. All objections to the claims and specification are withdrawn in view of Applicants respective amendments.

4. All 35 U.S.C. 112 2nd rejections are hereby withdrawn in view Applicants amendments to the claims.

5. The 35 U.S.C. 102(b) rejection of claims 4 and 17 is hereby withdrawn in view of Applicants amendments to the claims which specify that the derivatives are in crystalline form.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 112 – 1st

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement:

7. Claims 4, 7-10, 17-22 and new claims 62-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polyarginine human growth hormone (hGH) crystals made from the methods as stated in Examples 19, 21 or 27; *or* polyarginine hGH crystals which have a release profile wuch that aingle administration of said crystal to a mammal provies *in vivo* hGH serum concentration profiles in said mammal of a $T^{90\%}$ value of 74 hours versus a $T^{90\%}$ value of 20 hours for the same amount of soluble hGH, does not reasonably provide enablement for all polyarginine hGH crystals or crystal derivatives thereof with no specific characteristics or functions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In the instant case the claims are drawn to polyarginine crystals of human growth hormone (hGH) or hGH derivatives thereof. Upon reading the claims in light of the

specification, the claims are thus drawn to a huge number of hGH polyarginine crystals, wherein the specification only teaches how to make said crystals from two recombinant sources which are wild-type in form (e.g. Lucky Gold and Novartis rhGH, as used in Example 81). However, the crystallization of the two different forms, wherein one is recombinantly produced in yeast and the other in *E. coli*, say nothing about other isoforms or derivatives and the predictability of whether a skilled artisan could reproduce any of these crystals given the definitions in the specification without having to endure large amounts of undue experimentation.

The specification *only* sufficiently describes three polyarginine hGH crystal which meets the limitations of the claims (Examples 19, 21 and Example 27) and also which necessarily provides sufficient details and experimental data (see Tables 12, 13, 16-26) to ensure that a skilled artisan would not have to perform undue experimentation in order to achieve the stated *in vivo* limitations. The specification is void of any other types of polyarginine hGH crystals, but yet the scope of the claimed invention is drawn to any and every kind of polyarginine hGH crystals or derivatives thereof. It is sufficiently clear from the prior art that while human growth hormones have been successfully crystallized previously, that the variation of conditions from protein to protein is significantly different and the variation of particular "additives" or excipients can profoundly change the crystallization conditions as well as the *in vivo* functionality of the composition, such as the release profiles. What is successful for one growth hormone species (crystal or soluble) certainly is not for another species. Thus, a skilled artisan, in order to achieve that which falls within the metes and bounds of the instant

invention, would be required to determine both *de novo* processes to achieve successful crystallization conditions and crystals for each different polyarginine hGH crystal and derivatives thereof (e.g. any fragments, homologues, variants which are 2-100% identical to wild-type hGH of which are 5-45 kDa compared to wile-type) and subsequently to test each one to make sure it possesses the dependent claim limitations of particular bioavailability, serum concentrations which last for a particular time post administration. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The specification defines human growth hormone (hGH) and human growth hormone derivatives as follows (see pp. 11-12, paragraphs 0047-0048):

> "Human growth hormone (hGH)" denotes a protein having an amino acid sequence, structure and function characteristic of native human growth hormone. *As used herein, human growth hormone (hGH) also includes any isoform of native human growth hormone, including but not limited to, isoforms with molecular masses of 5, 17, 20, 22, 24, 36 and 45 kDa* [Haro et al., J. Chromatography B, 720, 39-47 (1998)]. Thus, the term hGH includes the 191 amino acid sequence of native hGH, somatotropin, and the 192 amino acid sequence containing an N-terminal methionine (Met-hGH) and somatrem [U.S. Pat. Nos. 4,342,832 and 5,633,352]. hGH may be obtained by isolation and purification from a biological source or by recombinant DNA methods. If made by recombinant DNA methodology, hGH is denoted as recombinant human growth hormone (rhGH). Met-hGH is typically prepared by recombinant DNA methodology.
>
> The term "human growth hormone derivative" refers to a protein having an amino acid sequence that is comparable to that of naturally occurring human growth hormone. *The term "comparable" refers to an amino acid sequence that is between **2% and 100% homologous to the 191 amino acid sequence of hGH** or the 192 amino acid-sequence of Met-hGH.*

Thus, nearly any hGH protein is encompassed within the claims. Those which are only 2% homologous, or identical, to native 191 amino acid hGH means that out of the 191 amino acids, only 4 need be the same. This would subsequently not even be expected to be an hGH protein, yet it is still is encompassed within the claims.

In the instant case, the quantity of experimentation would be considerable because the smallest change in *any* parameter in crystallizing a protein can have enormous consequences (e.g. temperature, salts, buffers, additional additives, different protein variants, etc.). Thus, it is not enough to have the crystallization conditions of a

related/similar protein or 'native' protein. Rather, what would be required is precise instruction about how to make the protein crystal (*each and every one*) in order to avoid undue experimentation. However, there is no direction or guidance in the specification of how a skilled artisan might achieve polyarginine crystals of *all* growth hormone proteins and *all* derivatives thereof, the only example which sufficiently meets this burden is Examples 21 and 27. The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a mutant or a protein complex even though they contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein complex) (see Weber, Overview of Crystallization Methods. Methods in Enzymology, 1997, Vol. 276, pp. 13-22). *At best*, the art of crystallization is unpredictable even to those skilled in the art who may either perform the experiments by hand or who are assisted by automated robotics because it often times requires thousands of individual experiments in order to find the one or two conditions that are successful for a single protein. Even then, there is no guarantee. It is even a well known fact in the art that luck often times play a fortuitous role in obtaining successful crystallization conditions despite the extremely high skill level of those in the art (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2). Furthermore, the prior art is of little assistance because there are so many different conditions which work for

different growth hormones (see for example, US Patents, 4,816,568; 5,633,352; 5,667,808; 5,734,026; 5,780,599; 6,022,858 and 6,117,984 – cited on the IDS from 11 Jan. 2005) but which are sufficiently different than the claimed invention, one skilled in the art understanding the unpredictability of the art, would have no reason to expect that other growth hormones other than hGH and, perhaps met-hGH, would reasonably produce polyarginine crystals with the stated limitations of the dependent claims. Thus, when all things are considered and the Wands factors are treated on their merits, the claim is not enabled because a great deal of undue experimentation would be expected and necessary in order to practice the full scope of claimed invention.

Written Description:

8. Claims 4, 7-10, 17-22 and new claims 60-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention,

> with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the

disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The specification fully and adequately describes how to make many different forms or species of hGH crystals, however, only three species of polyarginine hGH crystals. However, each and every crystal described in the specification was produced with native recombinantly produced proteins, either purchased from Novartis (produced in *E.coli*) or from Lucky Gold (produced in yeast). While it is readily apparent that these different forms of polyarginine hGH readily crystallize, no other hGH species or isoforms which fall within 5 kDa to 45 kDa of the 191 or 192 amino acid native hGH, nor any derivatives which are between 2% and 100% identical to the 191 or 192 amino acid native hGH are ever produced. Furthermore, none of these derivatives need have any sort of functionality whatsoever. And thus, the production of the polyarginine native hGH crystals (from Lucky Gold or Novartis) are not representative of the large and diverse genus encompassed by the claims.

In general, for a species of crystal to be adequately described, the following must be adequately disclosed in the specification and the claims: (1) the composition of the crystal (exact structural features of all molecules in the crystal must be described, including the protein/antibody (preferably a SEQ ID NO of all included residues) and any molecule bound to it) (2) the exact protein concentration and buffer the protein/antibody is in, (3) the exact temperature, buffers, salts, additives used for crystallization and 4) the technique used to obtain the crystal (e.g. vapor diffusion, microbatch, liquid-liquid diffusion, etc). The species noted in Examples 19, 21 and 27 have adequately met this

burden. However, the process of obtaining the crystals which is encompassed by the breadth of the claims is not described. In addtion, the crystals need not have any sort of functionality which describes the polyarginine hGH crystals, e.g. any particular release profiles or serum elevation profiles. A singular chemical composition can crystallize differently based on the crystallization conditions and techniques used and it is evident that each crystal type will have unique and different bioavailability characteristics. For example, if a skilled artisan wants to crystallize hGH for structural studies, then the crystallization technique, buffer considerations, temperatures, etc. are likely going to very different than when said artisan is trying to crystallize a protein for therapeutic use because the overall objectives are so different and the quality and quantity of the crystals are important but different for each. In addition, it is noted that there exists many different hGH crystals in the prior art which have different and unique serum elevation profiles and release profiles from the three disclosed polyarginine crystals. Thus, it is evident that hGH crystals and how they are made, and what protein they are made from is hugely significant in how the crystals behave *in vivo*.

Based on the instant the specification which does describe many different types of hGH crystal species, however, the crystal species are limited by only two different types of protein used in the production of the crystals (e.g. native hGH), the crystals produced encompassed by the breadth of the claims is unpredictable to one of skill in the art. Therefore, the claims drawn to the instant genera of hGH crystals are also not adequately described.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claim 4 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 7, 9 and 10 of copending Application No. 11/169,956 (US 2006/0008532). Although the conflicting claims are not identical, they are not patentably distinct from each other because of the many choices recited in the claims for what kind of protein is actually contained in the protein crystal of claim 1, and the many choices offered for the ionic compound the crystal is in complex with. Nonetheless, an obvious variation and choice of the many variations is a protein crystal of human growth hormone in complex with polyarginine which reads on instant claim 4.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

11. Applicant's arguments filed 05 February have been fully considered but they are not persuasive.

It is noted that Applicants arguments, which traverses the 35 U.S.C. 112 1st paragraph rejections regarding enablement and written description, have been taken into consideration. Specifically, Applicants arguments concerning the disclosure of the application and how the disclosure supports both written description and enablement can be summarized as (as noted on pp. 20, last line to p. 21, 1st paragraph): "In this application, Applicants teach methods of formulating hGH crystals for controlled release of hGH from its crystal lattice, regardless of what that lattice is or how it is formed. Applicants have crystallized hGH in multiple ways as shown in the examples, and when formulated with a polycation such as polyarginine, all of the formulations have improved release profiles. Thus, for both reason, the Examiner's focus on crystallization is misplaced and the § 112 rejections should be withdrawn."

However, the point which the Examiner still maintains is more emphasized above, specifically, Applicants have clearly noted and all the Examples found within the specification teaches how to produce hGH crystals from only the native proteins which have been recombinantly produced and purchased either from Lucky Gold or Novartis. However, the specification as noted above, specifically states: *As used herein, human*

growth hormone (hGH) also includes any isoform of native human growth hormone, including but not limited to, isoforms with molecular masses of 5, 17, 20, 22, 24, 36 and 45 kDa. Likewise, the definition of an hGH derivative is for the most part even broader by stating: "The term "human growth hormone derivative" refers to a protein having an amino acid sequence that is comparable to that of naturally occurring human growth hormone. *The term "comparable" refers to an amino acid sequence that is between* ***2% and 100% homologous to the 191 amino acid sequence of hGH*** *or the 192 amino acid-sequence of Met-hGH"* (see p. 11-12, paragraphs 0047-0048). However, it is noted that Applicants are not in possession of more than two species of the soluble protein, e.g. Lucky Gold rhGH or Novartis rhGH, let alone any others which are in crystalline form, and likewise the disclosure does not adequately teach a skilled artisan how to make these other hGH crystalline species. The specification states that by making the crystals from two different sources, this suggests that rhGH will have the same crystallization and solubility characteristics. However, this is not convincing because the two sources use native recombinant hGH only, while the claims encompass any hGH crystal or crystal derivative complexed to polyarginine and there is no functional requirement for the crystalline polypeptides. Even in the claims where an attempt at making some sort of functional limitation it is so broad that it is almost non-limiting. E.g. claim 7 states that the $T^{90\%}$ need for the crystalline hGH need be only at a value higher than provided by a single administration of the same amount. But how much higher? Claim 8 suffers from the same deficiencies. Page 70 of the specification gives examples of how much higher for the $T^{90\%}$ as being significantly higher compared

to the soluble hGH, being 20 hours for soluble and 74 hours of the polyarginine complexed crystals. Such limitations thus meet the requirement for structure and function for written description and enables the claims in light of the specification. However, the broadness, unpredictability of structure *and* function of the claims as they stand far exceed that which is enabled in the specification.

Furthermore, it is noted that there are no derivatives or fragments, isoforms or homologues thereof which are 2-99% identical to native hGH anywhere in specification, nor are there any which only must adhere to the non-descript molecular weight limitations that can be as small as 5 kDa compared with the wild-type 45 kDa molecular weight. Thus, it is deemed that Applicants have not provided enough hGH species in crystalline form which are non-native in order to claim the entire genus of polyarginine hGH crystals which includes any hGH isoforms as small as 5 kDa and as large as 45 kDa or having as little as 2% identity to the 191 or 192 amino acid native hGH proteins (which means a protein which would have 191 amino acids, but only 4 of those amino acids need to be identical to hGH). Nor are the claims enabled given their breadth and the unpredictability of producing any polyarginine hGH crystal which may or may not necessarily have any sort of function whatsoever. Therefore, Applicants neither are in possession of the claimed genus, nor are they enabled for the breadth of the claim which also covers the same species because, for example, it would be highly unpredictable and unlikely that a protein with only 4 amino acids in common with native hGH would crystallize in the same conditions disclosed in the specification and thus

there would be a considerable expectation that an unreasonable amount of undue experimentation would be expected by one skilled in the art.

Conclusion

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN
24 April 2007

KATHLEEN KERR BRAGDON, PH.D.
SUPERVISORY PATENT EXAMINER